CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
OCTYL-BICYCLOHEPTENE-DICARBOXIMIDE (MGK 264)

Chemical Code # 000396, Tolerance # 00367
SB 950 # 082

Sept. 24, 1987
Revised: 6/1/88; 8/8/89; 10/20/94, 8/17/95, 7/18/97

I. DATA GAP STATUS

Combined rat (chronic + onco):	No data gap, possible adverse effect (onco)
Chronic dog :	No data gap, no adverse effect
Onco mouse :	No data gap, possible adverse effect
Repro rat :	No data gap, no adverse effect
Terato rat :	No data gap, no adverse effect
Terato rabbit :	No data gap, no adverse effect
Gene mutation :	No data gap, no adverse effect
Chromosome :	No data gap, no adverse effect
DNA damage :	No data gap, no adverse effect
Neurotox :	Not required at this time

Note: Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name: T970818.

Prepared by Aldous 9/24/87, Silva, 6/1/88; Revised: Chernoff, 8/8/89; Updated by P. Iyer, 10/20/94, 8/17/95, 7/18/97.

Record numbers through volume 367-043 and 145097 listed by the Pesticide Registration Library have been rectified with those listed in the Toxicology Summary.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY SUMMARY

COMBINED, RAT

****026 126730**, "24 Month Dietary Chronic Toxicity and Oncogenicity Study in the Rat with MGK-264", (Edwin I. Goldenthal, International Research and Development Corporation, MI., Report # 551-030, 10/8/93). Test article is identified as MGK 264 Insecticide Synergist (N-Octylbicyloheptene Dicarboximide) with 90.76% purity. 60 Charles River CD* rats per sex per group received 0 (Purina Certified Rodent Chow* #5002), 50, 150, and 450 mg/kg/day in the diet for 24 months. Increased absolute and relative liver weights are noted for both sexes at 150 and 450 ppm. In the liver, increased incidence of hepatocellular hypertrophy (mid and high dose, both sexes), bile stasis (high dose, both sexes), bile duct cysts at high dose (males and females), eosinophilic altered foci (high dose, males), and clear cell altered foci (high dose, both sexes) are indicated. Microscopy also revealed increased brown pigment in the kidney of both sexes at the high dose level. **Possible adverse effect**: a slight increase in follicular adenomas of the thyroid in males at 50, 150, and 450 mg/kg/day. Chronic NOEL = 150 mg/kg/day (9% to 23% reduction in bodyweights for both sexes at 450 mg/kg/day). Oncogenicity NOEL < 50 mg/kg/day. **Acceptable**. (H. Green and P. Iyer, 10/25/94).

CHRONIC, RAT

008 035840, "MGK-264 Feeding Study (Rats)", (Wisconsin Alumni Research Foundation, 1964). Octylbicycloheptene dicarboximide, no purity given, was administered to Sprague Dawley rats in the diet for 2 years at 0, 62.5, 250 or 1000 ppm, 10/sex/group. No adverse effect indicated. UNACCEPTABLE. not upgradeable**.** Too few animals, no blood chemistry, inadequate histology exams, data poorly organized, dose levels not justified, test article not characterized. (J. Christopher, 4/2/85, and C. Aldous, 10/30/85).

001 020179. Summary report of 008 035840. This summary was the version reviewed by J. Christopher on 4/2/85.

001 069377. Brief summary of 035840.

367 032 136075, "13 Week Dietary Range-Finding Toxicity Study in Rats with MGK® 264 Insecticide Synergist", (Malcolm Blair, IRDC, MI, Report # 551-028, 10/18/89), N-octyl bicycloheptene dicarboximide, 98% purity, fed in the diet concentrations of 0 (Ralston Purina Certified Rodent Chow® #5002), 125, 250, 500, 1000, and 2000 mg/kg/day with 10 Charles River CD® rats/sex/group.
3 males and 6 females died or were killed in extremis at the 2000 mg/kg/day. Rats from the 2000 mg/kg/day group were removed from test material and were given access to basal diet. 4 remaining animals (2 male, 2 female) in the 2000 mg/kg/day group were moribund and demonstrated labored breathing and were pale and cold to touch. Body weight reduction of more than 10% was noted at both 1000 mg/kg/day and the 2000 mg/kg/day groups in both sexes. Food consumption was lowered in males at 2000 mg/kg and at 500, 1000, and 2000 mg/kg/day in females. Absolute and relative liver weights in females were consistently increased in males and females at 250, 500, and 1000 mg/kg, however no other lesions were noted. Histopathology was not performed and hematology revealed no treatment-related changes. **Adverse effects are not indicated**. NOEL = 125 mg/kg/day (increased liver weights at 250, 500 and 1000 mg/kg/day). It is considered **supplemental** information for SB950/550 purposes. No worksheet (P. Iyer 8/11/95).

CHRONIC, PIG

008 035839, "Two Year Chronic Toxicity - MGK 264 (Octylbicycloheptene dicarboximide) - Miniature Breed Swine", (Harris Labs, 3/2/65). Octylbicycloheptene dicarboximide, no purity given, was fed to a miniature breed of pigs, 3 per sex per dose group, in the diet at 0, 25, 100 or 300 ppm. No adverse effect indicated. UNACCEPTABLE**,** not upgradeable**.** Dose levels not justified and no toxicity at highest dose tested, too few

animals, no clinical observation data, inadequate histology exams, limited blood chemistry evaluation. (J. Christopher, 4/3/85, and C. Aldous, 10/30/85).

001 020180. Series of interim reports related to 008:035839. This summary was the version reviewed by J. Christopher on 4/3/85.

CHRONIC, DOG

021 112198, "One Year Dietary Toxicity Study in Dogs with MGK-264", (Malcolm Blair, International Research and Development Corporation, MI. Report # 551-031, 12/16/91). MGK 264 Insecticide Synergist (N-Octylbicycloheptene dicarboximide) with 92.26% purity was administered to purebred Beagle dogs (4 per sex per group) at 0, 65, 250, and 1000 ppm in the diet (Purina Certified Canine Diet #5007) for one year. Food consumption values were increased in all treated groups. While the increase in absolute and relative liver weights was not statistically significant, a brown pigment was noted in the liver of both sexes at 1000 ppm and hepatocellular hypertrophy was also recorded in high dose males (50%). **Adverse effects are not indicated. NOEL = 250 ppm (hepatic effects). Acceptable (H. Green, and P. Iyer, 10/25/94).

025 126720, "Two Month Dietary Range-Finding Toxicity Study in Dogs with MGK® 264", (Malcolm Blair, International Research and Development Corporation, MI., Report # 551-029). Test article is identified as MGK 264 (N-Octyl bicyclo heptene dicarboximide) with 98% purity. 2 Purebred Beagle dogs per sex per group received 0, 65, 125, 250, 1000 and 4000 ppm in the diet (Purina Certified Canine Diet® #5007) for 61 days. Bodyweights were slightly reduced (not statistically significant) for males at 125, 250, 1000 and 4000 ppm; for females at 1000 and 4000 ppm. Food consumption was sporadically decreased for high dose males and females. **Supplemental**. No worksheet (H. Green and P. Iyer, 1/25/94).

367-020 112197 Duplicate of 025 126720

ONCOGENICITY, RAT
See Combined Rat above.

ONCOGENICITY, MOUSE

018 093438, 093439, "Eighteen Month Dietary Oncogenicity Study in Mice with MGK® 264 Insecticide Synergist", (Malcolm Blair, IRDC, MI. 49071, Report # 551-011, 13 June 1991), N-octyl bicycloheptene dicarboximide, 98% purity, administered in the diet for 18 months at 0 (Ralston Purina Certified Rodent Chow* #5002), 50, 400 and 800 mg/kg/day to 50 Charles River CD-1® mice/sex per group. Body weight reduction (3% to 5.5%), is noted for males at 400 and 800 mg/kg/day. Necropsy revealed increased absolute liver/gallbladder weights for males and increased liver/gallbladder/body weight ratios for both sexes at 400 and 800 mg/kg/day. Macroscopic examination also revealed an increased incidence of liver nodules/masses in males at 400 and 800 mg/kg/day. Histopathology result indicate increased incidences of hepatic hypertrophy, hepatocellular adenomas, hyperplastic nodules and hepatic calculi in 400 mg/kg/day and 800 mg/kg/day males and bile stasis and gallbladder calculi at 400 and 800 mg/kg/day in both sexes. **Adverse effects are indicated**. Chronic NOEL = 50 mg/kg/day (reduced body weights at 400 and 800 mg/kg/day, increased liver weight and hypertrophy). Oncogenicity NOEL = 50 mg/kg/day (hepatocellular adenomas in 400 and 800 mg/kg/day males). **Acceptable**. (H. Green, and P. Iyer, 9/16/94).

017 093437, "13 Week Dietary Range-Finding Toxicity Study in Mice with MGK® 264 Insecticide Synergist", (Malcolm Blair, IRDC, MI, Report # 551-010, 2/4/87), N-octyl bicycloheptene dicarboximide, 98% purity, fed in the diet concentrations of 0 (Ralston Purina Certified Rodent Chow® #5002), 125 (increased to 4000

beginning study week 7), 250, 500, 1000, and 2000 mg/kg/day with 10 Charles River CD®-1 mice/sex/group. 2 males were found dead at 125/4000 mg/kg/day and 1 female was sacrificed in extremis. Decreased defecation was noted at 2000 and 125/4000 mg/kg/day; dark yellow urine, firm areas in abdomen, tremors, yellow material on anogenital region, reduced motor activity, labored breathing, and coolness to touch were noted at 125/4000 mg/kg/day. Statistically significant male bodyweight reduction at 125/4000 mg/kg/day from week 7 to study termination. Compared to control group a statistically significant increase in male relative liver weights is noted at all dose levels of the chemical. Histopathology revealed cholangiofibrosis and portal bile duct proliferation at 125/4000 and 2000 mg/kg/day in both sexes. **Adverse effects are not indicated**. NOEL = 1000 mg/kg/day (decreased defecation at 2000 and 125/4000 mg/kg/day). It is considered **supplemental** information for SB950/550 purposes. No worksheet (H. Green and P. Iyer 10/18/94).

REPRODUCTION, RAT

009 035841, "Three Generation Teratogenic Study with MGK 264 Insecticide Synergist - Effects on Rat (Sherman-Wistar) Reproduction", (Industrial Biology Laboratories Inc., 12/21/65). Octylbicycloheptene dicarboximide, no purity given, was fed in the diet to Sherman-Wistar rats at (nominally) 0, 35, 350, or 3500 ppm, 10 males and 20 females/group. UNACCEPTABLE, unlikely to be upgradeable**.** Lack of diet analysis, no clearly established toxicity at high dose and no clinical observation data to substantiate adequacy of dose levels. Adults which failed to successfully mate were not examined to find cause of failure. (J. Christopher, 4/2/85 and C. Aldous, 10/25/85).

001 904700. Summary of 009 035841. This summary was the version reviewed by J. Christopher on 4/2/85.

367-031 136074 "Data from dose group 20000 ppm from two generation rat reproduction study". 26 males and females were dosed with 20000 ppm of MGK in the diet. One male and 4 females died after 3 weeks of exposure and 25 males and 22 males died after 4 weeks of exposure. Autopsy results revealed hydrohephrosis, multiple foci in kidneys, distended urinary bladder and other lesions of excessive toxicity. No worksheet (P. Iyer, 8/11/95).

** 019, 030 112035, 136070, "Two-Generation Reproduction Study of MGK® 264 in the Albino Rat", (James L. Schardein, IRDC, MI. Report # 551-027, 12/18/91 and 4/12/95), the test article MGK® 264 Insecticide Synergist (100% purity) was administered in the diet through two generations (2 litters per generation) at 0 (Purina Certified Rodent Chow® #5002), 1250, 2500, and 10000 ppm to Charles River COBS® CD® rats 26/sex/group. The animals in the 1250 ppm group were from a different population, began treatment with a lower initial body weight, approximately 2-months after other animals and did not have a concurrent control group. The group mean body weights of both parental F0 and F1 animals were reduced compared to the controls at 2500, and 10000 ppm. Histopathology of hepatic tissue revealed increased incidences of brown pigment, portal bile duct proliferation, hyaline droplets, and calculi in F0 and F1 parents (males and females) at 10000 ppm, and increased hepatocellular hypertrophy in both 2500 and 10000 ppm groups. Upon reconsideration the reviewer decided not to include the 1250 ppm population since it did not have a concurrent control. Parental NOEL < 2500 ppm, NOAEL = 2500 ppm. Reproductive NOEL = 2500 ppm (statistically significant reduced pup weights at 10000 ppm). Initially reviewed as unacceptable (H Green and P. Iyer, 10/20/94). Upgraded to acceptable upon submission of certificate of analysis for the test article (367-030), and data from range-finding study (367-032) to support rationale for dose selection. P. Iyer, 8/17/95.

TERATOGENICITY, RAT

009 035843, "Effect of Technical MGK 264 (Octylbicycloheptene dicarboximide) on the Embryonic Development of Rats". (International Bio-Research, Inc., 4/76). Octylbicycloheptene dicarboximide, purity not stated, was administered by gavage to pregnant Wistar rats on day 5 to 15 of gestation at 0 (methyl cellulose), 40, 200 or 1000 mg/kg/day, 20/group. Maternal NOEL = 200 mg/kg/day, sedation, slow reflexes; Developmental toxicity NOEL = 40 mg/kg/day, ossification delays and increased resorptions, **a possible adverse effect.** UNACCEPTABLE**.** No analysis of dosing solutions and inadequate characterization of test article, some additional deficiencies as indicated in 10/24/85 review. (J. Christopher, 4/2/85, and C. Aldous, 10/24/85).

001 904699. Summary of 009 035843. This summary was the version reviewed by J. Christopher on 4/2/85.

014 088791, "Range-Finding Developmental Toxicity in Rats", (J. L. Schardein, International Research and Development Corp., Laboratory Project I. D. No. 551-025, August 17, 1989). MGK® 264, 98.0% purity, administered by gavage at concentrations of 250, 500, 1000, 1500, or 2000 mg/kg to 5 Charles River COBS® CD® mated female rats on days 6 through 15 of gestation. Another group of 5 rats administered 0.5% methylcellulose (10 ml/kg/day) served as controls. Maternal NOEL = questionable, data on body weight gain not statistically analyzed; reduced body weight gain is indicated at all dose levels and most apparent at and above the 1000 mg/kg/day dose levels. **Adverse effect**: Maternal mortality and increased post-implantation loss for the high dose group. Developmental NOEL = 1500 mg/kg/day. UNACCEPTABLE (data lacks statistical analysis and antemortem data reported in an inconsistent manner (J. Kishiyama and P. Iyer, 9/13/94).

**014 088792, "Developmental Toxicity in Rats", (J. L. Schardein, International Research and Development Corp., Laboratory Project I. D. No. 551-026, June 8, 1990). MGK® 264, 98.0% purity, administered by gavage at concentrations of 100, 300, or 1000 mg/kg to 25 Charles River COBS® CD® mated female rats/group on days 6 through 15 of gestation. Another group of 25 rats administered 0.5% methylcellulose (10 ml/kg/day) served as controls. Maternal NOEL = 300 mg/kg/day (increased salivation and depressed [>25%] body weight gain). Developmental NOEL = >1000 mg/kg/day (limit test): no significant variations or malformations of the fetuses were reported. ACCEPTABLE (J. Kishiyama and P. Iyer, 9/13/94).

This study 014 088792 is acceptable and replaces the previous study 009 035843 reviewed 10/24/85.

TERATOGENICITY, RABBIT

** 010 063389 "Teratological Study of MGK 264 Insecticide Synergist Administered Orally to Albino Rabbits," (IRDC, 8/31/87). MKG 264 (purity = 98%, lot no. 3843), was administered by gavage to inseminated New Zealand White SPF rabbits (16/group) at 0 (vehicle = 0.5% methylcellulose), 10, 30 and 100 mg/kg/day during days 7 to 19 of gestation (day of insemination = day 0 of gestation). Maternal NOEL = 100 mg/kg (no significant effects observed). Developmental NOEL = 100 mg/kg (No adverse effect). The study was reviewed as unacceptable (M. Silva, 5/23/88), and the pilot study used for dose justification was requested. The pilot study (record #068564) was evaluated and the data found adequate to upgrade this main study to acceptable status.
(Chernoff 8/8/89).

012 068564 "Range-Finding Teratology Study in Rabbits with MGK 264 Insecticide Synergist", (IRDC, 12/3/86). MGK® 264 insecticide synergist, 98% pure in aqueous solution was administered by gavage to

groups of 5 pregnant New Zealand rabbits at concentrations of 0 (deionized water), 300, 600, 900, 1200 or 1500 mg/kg/day on days 7 through 19 of gestation. Possible adverse effects at the high doses in this study include: maternal toxicity of the gastrointestinal system as evidenced by decreased weight gain, decreased fecal material, blood in cage pan, and necropsy observations of gastric irritation; increased maternal morbidity and mortality; increased incidence of spontaneous abortions and resorbed litters; and a decrease in fetal viability. Developmental NOEL < 300 mg/kg (resorptions, stillbirths, no viable fetuses). Maternal NOEL < 300 mg/kg (decreased body weight, abortions, gastrointestinal toxicity). Supplemental to 063389. (Chernoff, 8/7/89)

GENE MUTATION

** 011 063385, "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)", (Microbiological Associates, Inc., 9/16/86). MGK 264 containing octyl-bicycloheptene-dicarboximide (purity = 98%, lot no. 3843), was used in a mutagenicity assay (triplicate plates) with tester strains TA100, TA98, TA1535, TA1537 and TA1538 at 0 (negative control vehicle = acetone), 10, 33, 100, 333, 1000, 3333 and 10,000 ug/plate with and without activation. There were no effects observed at any dose with any of the tester strains. No adverse effect. ACCEPTABLE. (M. Silva, 5/25/88).

** 011 063388, "L5178 TK+/- Mouse Lymphoma Mutagenesis Assay", (Microbiological Associates, Inc., 12/15/86). MGK 264 containing octyl-bicycloheptene-dicarboximide (purity = 98%, lot 3843) with and without Aroclor induced rat liver S-9 was placed on L5178Y TK+/- cells at 0 (vehicle = acetone), 0.0013 to 0.018 (no S-9) or 0.0042 to 0.059 (+S-9). An initial mutagenicity assay was rerun due to equivocal results, therefore two trials were reported in this study. 48 Hours after exposure, cells were cloned and either exposed to TFT 3 ug/ml (3 plates/culture) or plated in cloning medium for viable cell counts for 10-12 days. No adverse effect**.** No mutagenicity was observed at any dose level when the test was repeated. ACCEPTABLE (M. Silva, 5/27/88).

CHROMOSOME

** 011 063386, "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells with a Confirmatory Assay", (Microbiological Associates Inc., 1/14/87. MGK 264 containing octyl-bicycloheptene-dicarboximide (purity = 98%, lot 3843) was used on Chinese hamster ovary (CHO-K1) cells at 0 (vehicle = acetone), 0.005, 0.01, 0.02, 0.04 ul/ml--(no activation) and 0, 0.01, 0.02, 0.04, 0.06, 0.08 ul/ml (activation). No chromosomal effects were observed at any dose. Toxicity was observed with activation at doses > 0.04 ul/ml. No adverse effect. ACCEPTABLE. (M. Silva, 5/26/88).

DNA DAMAGE

** 015 095480, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes" (R.D. Curren, Microbiological Associates, Laboratory Project ID T5 205.380026, 11/7/90). MGK* 264, purity 93.1%, was used in an unscheduled DNA synthesis assay on primary rat hepatocytes derived from Fischer-344 rat livers. Three replicate plates were treated with 0 (vehicle = acetone), 0.001, 0.003, 0.01, 0.02 and 0.03 ul/ml for 18-20 hours. No significant increase in UDS (i.e., no significant increases in net nuclear count of silver grains) was observed at any dose level. **No adverse effect. Acceptable** (J. Kishiyama and P. Iyer, 8/25/94).

** 011 063387, "Unscheduled DNA Synthesis in Rat Primary Hepatocytes", (Microbiological Associates, 4/20/87). MGK 264 containing octyl bicyclo-heptene dicarboximide (purity = 98%, lot 3843) was used in an unscheduled DNA synthesis assay on primary rat hepatocytes derived from Fischer-344 and Sprague-Dawley rat livers. Three replicate plates were treated with 0 (vehicle = acetone), 0.0003, 0.001, 0.003, 0.01, and 0.03

ul/ml for 18-20 hours. No significant increase in UDS was observed at any dose level. No adverse effect. ACCEPTABLE. (M. Silva, 5/26/88).

NEUROTOXICITY Not required at this time.

SUPPLEMENTAL

033-145087 MGK-264 [Hexyl-1-^{14}C]: Absorption, Distribution, Metabolism and Excretion Studies in Rats. Study No. P01932. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 3/20/92). MGK-264 [Hexyl-1-^{14}C] (unlabeled MGK 264: Lot# 3843, 93.1% purity), s.a.:18.4 mCi/mmol, 98.3% radiopurity). 5 Sprague-Dawley rats/sex were treated with single (100 or 1000 mg/kg) or multiple doses (pretreated daily with 100 mg/kg unlabeled MGK-264 for 14 days followed by a single dose of radiolabeled [Hexyl-1-^{14}C] MGK-264). Blood levels of radioactivity for male rats peaked ~ 4 hours after dosing and for females ~ 6 hours after dosing. The blood half-life was calculated to be ~ 6 hours for females and ~ 8 hours for males. Following single and multiple dose administration at 100 mg/kg, 49.49-73.05% and 20.87 -46.67% of the radiolabel was eliminated in the urine and feces, respectively. The total mean recovered radioactivity of the administered dose in the three groups ranged between 93.13%-97.43%. The pattern of excretion of radioactivity in urine and feces within each sex was similar. However, the female rats in each dose group excreted approximately 10-20% more of the total radioactivity in the urine than the males while the male rats in each dose group excreted approximately 10-20% more of the total radioactivity in the feces than the females. Tissue residues of ^{14}C were negligible (less than 0.43% of the administered dose) in all groups. Acceptable. (P. Iyer, 5/12/97).

034-145088 Addendum to Report Entitled "Absorption, Distribution, Metabolism and Excretion Studies of [Hexyl-1-^{14}C] MGK-264 in Rats." Addendum to Study No. P01932. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 3/9/93). MGK-264 [Hexyl-1-^{14}C], (unlabeled MGK 264 lot # 3843; 93.1 % purity) s.a.:18.4 mCi/mmol, 98.4% radiopurity. 5 Sprague-Dawley rats/sex were treated with single (100 or 1000 mg/kg) or multiple doses (pretreated daily with 100 mg/kg unlabeled MGK-264 for 14 days followed by a single dose of radiolabeled [Hexyl-1-^{14}C] MGK-264). Metabolic profile of the ^{14}C residues in the urine and extracts of fecal samples (extracted with water and methanol) from the ADE study were determined using HPLC. Additional male and female rats (8/sex) were orally dosed with [Hexyl-1-^{14}C] MGK-264 at 859 mg/kg and 697 mg/kg to generate urinary and fecal ^{14}C residues for qualitative analysis. Major metabolites from 0-24 hour urine samples collected from males and had similar retention times as the four metabolites previously observed in rats dosed with [Norbornene 2,3-^{14}C] MGK 264 (036 145090). The percentage of polar metabolites resulting from the β-oxidation was higher in males (53.6% - 62.41%) than females (34.79% - 42.75%), while less polar metabolites in urine or feces resulting from ω-oxidation was higher in females (44.72% - 59.34) than males (30.93% - 37.03%) indicating a sex difference in the quantitative metabolism of MGK-264. Acceptable. (P. Iyer, 5/27/97).

035-145089 MGK-264 [Norbornene-2,3 -^{14}C]: Absorption, Distribution, Metabolism and Excretion in Rats. Study No. P01933. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 12/23/91). MGK-264 [Norbornene-2,3 -^{14}C] (Lot# 3843 93.1% purity), s.a.:26.0 mCi/mmol, (99.8% radiopurity). 5 Sprague-Dawley rats/sex were treated with single (100 or 1000 mg/kg) or multiple doses (pretreated daily with 100 mg/kg unlabeled MGK-264 for 14 days followed by a single dose of radiolabeled [Norbornene-2,3 -^{14}C] MGK-264). Blood levels of radioactivity for male rats peaked ~ 4 hours after dosing for males and ~ 6 hours after dosing for females. The blood half-life was calculated to be ~ 4.2 hours for males and ~ 3.5 hours for females. Most of the radioactivity recovered was excreted during the first 24 hours in the urine and during the first 36 hours for the

feces following administration. Following single and multiple dose administration at 100 mg/kg, 41.84-68.25% of the radiolabel was eliminated in the urine and 25.28-51.90% in feces. The total mean recovered radioactivity of the administered dose in the three groups ranged between 93.53%-99.88%. Radioactivity appeared to be more rapidly absorbed from the male gastrointestinal tract than that of females, however the blood radioactivity half-lives suggest that radioactivity was more rapidly eliminated by the females than the males. The pattern of excretion of radioactivity in urine and feces within females was similar with the female rats in the low dose groups excreting approximately 22-24% more of the total radioactivity in the urine than the males. However, the male rats in single oral high dose group were similar to the females. Additionally males in all groups excreted approximately 10-20% more of the total radioactivity in the feces than the females and retained more radioactivity in the liver and intestines than females. Thus [Norbornene-2,3 -^{14}C] MGK-264 appeares to undergo entero-hepatic circulation at different rates in the males and females, with females excreting it more rapidly in the urine than males. Acceptable. (P. Iyer, 6/2/97).

036-145090 Addendum to Report Entitled "Absorption, Distribution, Metabolism and Excretion Studies of [Norbornene-2-3,-^{14}C] MGK-264 in the Rat." Addendum to Study No. P01933. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 3/3/93). MGK-264 [Norbornene-2-3,-^{14}C] (unlabeled MGK: Lot# 3843, 93.1% purity), specific activity:26.0 mCi/mmol, 99.7% radiopurity). 5 Sprague-Dawley rats/sex were treated with single (100 or 1000 mg/kg) or multiple doses (pretreated daily with 100 mg/kg unlabeled MGK-264 for 14 days followed by a single dose of radiolabeled [Norbornene-2-3,-^{14}C] MGK-264). Metabolic profile of the ^{14}C residues in the urine and extracts of fecal samples (extracted with water and methanol) from the ADE study were determined using HPLC. Additional male and female rats (5/sex) were orally dosed with [Norbornene-2-3,-^{14}C] MGK-264 at ~ 1000 mg/kg to generate urinary and fecal ^{14}C residues for qualitative analysis. The four major metabolites isolated and identified in the urine were carboxylic acids produced by either β-oxidation or ω-1 oxidation of the side chain and epoxides which were formed by oxidation of the norbornene double bond. A minor metabolite identified as a carboxylic acid with an intact norbornene ring was also found. Males excreted more of the administered dose as polar metabolites in the feces (26.35% - 31.05%) than females (12.57% -14.48%), while less polar metabolites in urine resulting from ω-1 oxidation was higher in females (45.96% - 52.43%) than males (19.98% - 33.92%) indicating a sex difference in the quantitative metabolism of MGK-264. Acceptable. (P. Iyer, 6/5/97).

037-145091 Determination of Expired $^{14}CO_2$ Following Oral Dosing of [Hexyl-1-^{14}C] MGK-264 in the Rat. Study No. P01931. S. Selim, Ph.D., Biological Test Center, Irvine, CA 92713., conducted for MGK Company, Martinez, CA 94553. Final Report Date: 1/16/91). MGK-264 [Hexyl-1-^{14}C] (Lot# CFQ 6188, 99.0% purity, s.a.:18.4 mCi/mmol). 2 Charles River CD rats/sex were treated with single dose (100 mg/kg) of radiolabeled [Hexyl-1-^{14}C] MGK-264 by oral gavage. After dosing, animals were placed in Roth metabolism cages and expired $^{14}CO_2$ was collected in a gas trap containing ethanolamine/cellusolve (2/1;V/V). Samples were collected at 2, 4, 8, 24 and 48 hours after dosing and the ^{14}C radioactivity was measured. After 48 hours the ^{14}C radioactivity recovered from the male/female rats averaged 0.02% of the total dose. These results demonstrate that [Hexyl-1-^{14}C] MGK-264 undergoes very little metabolic degradation to $^{14}CO_2$ in these rats. Acceptable. (P. Iyer, 6/9/97).

038-145092 Determination of Expired $^{14}CO_2$ Following Oral Dosing of [Norbornene-2,3-^{14}C] MGK-264 in the Rat. Study No. P01930. S. Selim, Ph.D., Biological Test Center, Irvine, CA 92713., conducted for MGK Company, Martinez, CA 94553. Final Report Date: 5/22/91). MGK-264 [Norbornene-2,3-^{14}C] (Lot# CFQ 6189, specific activity:15.2 mCi/mmol, 98% purity). 2 Charles River CD rats/sex were treated with single dose (~100 mg/kg) of radiolabeled [Norbornene-2,3-^{14}C] MGK-264 by oral gavage. After dosing, animals were placed in Roth metabolism cages and expired $^{14}CO_2$ was collected in a gas trap containing ethanolamine/cellusolve (2/1;V/V). Samples were collected at 2, 4, 8, 24 and 48 hours after dosing and the ^{14}C radioactivity was measured. After 48 hours the^{14} C radioactivity recovered from the male/female rats averaged 0.00% of the total dose. These results demonstrate that [Norbornene-2,3-^{14}C] MGK-264 undergoes very little measurable metabolic degradation to $^{14}CO_2$ in these rats. Acceptable. (P. Iyer, 6/10/97).

039-145093 Pharmacokinetic and Distribution Studies of [Hexyl -1-^{14}C] MGK-264 (endo/exo mixture) in the Rat Following Dermal Administration. Study No. P02072. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 5/6/92). MGK-264 [Hexyl-1-^{14}C] (Lot# 3843, 93.1% purity), s.a.:18.4 mCi/mmol, 98.3% radiopurity) was administered dermally to 5 male rats as a 5% (w/w) solution in isopropanol. A mean single dose of 13.64 mg/kg was achieved. Blood samples were collected over 120 hours at regular intervals to determine levels of radioactivity. Blood levels of radioactivity for male rats peaked at ~ 6 and 12 hours after dosing and the half-life was 31.17 hours. Additionally, 5 male rats/group were administered the ^{14}C MGK-264 as a 5% solution and euthanized at peak blood level (12 hours), blood half-life (hour 43), second half-life (hour 74) and at 168 hours post -dose. Necropsies were conducted and tissues, urine and feces were examined for levels of radioactivity. The treated skin and enclosures glued on to the treated skin area were also removed and rinsed and the rinses were measured for radioactivity. The mean amounts of radioactivity in the skin rinse at the four time points were 81.07%, 53.06 %, 29.96% and 0.62% respectively. The radioactivity from the carcass decreased at the 168 hour euthanasia interval suggesting a lack of accumulation in tissues examined. The occurrence of two peaks and the presence of radioactivity in the intestines, liver and feces indicate involvement of the enterohepatic circulation in the elimination of MGK 264. Supplemental (P. Iyer, 7/1/97).

040-145094 Pharmacokinetic and Distribution Studies of [Hexyl -1-^{14}C] MGK-264 (endo/exo mixture) in the Rat Following Multiple Dermal Administration. Study No. P02073. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 7/27/92). Multiple doses of unlabeled MGK-264 for 14 days followed by a single dose of MGK-264 [Hexyl-1-^{14}C] (Lot# 3843, 93.1% purity, s.a.:18.4 mCi/mmol, 98.3% radiopurity) were administered dermally to 5 male rats as a 5% (w/w) solution in isopropanol. Blood samples were collected over 120 hours at regular intervals to determine levels of radioactivity. A mean dose of 12 mg/kg in 100 µl with 13.9 - 14.5 µCi was acheived. Blood levels of radioactivity for the rats peaked at ~ 6 and 10 hours after dosing and the half-life was 28.5 hours. Additionally 5 male rats/group were administered multiple doses of MGK 264 followed by a single dermal dose of the ^{14}C MGK-264 as a 5% solution (12 mg/kg/body weight) and euthanized at peak blood level (12 hours), blood half-life (hour 43), second half-life (hour 74) and at 168 hours post -dose. Also one group of 5 females were similarly treated to 17 mg/kg and euthanized at 168 hours post-dose. Necropsies were conducted and tissues, urine and feces were examined for levels of radioactivity. The treated skin and enclosures glued on to the treated skin area were also removed and rinsed and the rinses were measured for radioactivity. The mean amounts of radioactivity in the skin rinse at the four time points were 71.85%, 49.54%, 37.54%, 8.09% and 0.44 % (females) respectively. The radioactivity from the carcass decreased at the 168 hour euthanasia interval suggesting a lack of accumulation in tissues examined. The occurrence of two peaks and the presence of radioactivity in the intestines, liver and feces indicate involvement of the enterohepatic circulation. Supplemental (P. Iyer, 7/7/97).

041-145095 Absorption and Mass Balance of ^{14}C MGK-264 After Topical Administration to Healthy Volunteers. Study No. P02057. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 6/18/92). Four healthy male volunteers were dermally administered 5 mg (~ 50 µCi) of ^{14}C labelled MGK-264 (Lot# 3843, 93.1% purity, s.a.:18.4 mCi/mmol, 98.3% radiopurity) to a 4 x 6 cm area on the volar aspect of the forearm. The area had a non-occlusive cover and 8 hours after application the dose was removed by wiping dosed area with isopropyl alcohol swabs. Blood samples were collected from both forearms (ipsilateral and contralateral) over 120 hours at regular intervals to determine levels of radioactivity in plasma. Urine and fecal samples were collected for 5 consecutive days and the skin was stripped (tape stripping) with 3M tape at 1, 23 and 45 hours after removal of the dosage. A mean of 1.67% of the administered radioactivity was excreted in the urine, with no measurable amount in the feces. A total mean of 91.71 % was recovered with 88.72% being “external”. The tape stripping revealed that radioactivity did not accumulate in the skin. HPLC analysis of the

urine demonstrated that the MGK 264 was extensively metabolized, however evaluation of metabolism does not match previous reports (036-145090). No worksheet. Supplemental (P. Iyer, 7/14/97).

042-145096 Absorption and Mass Balance of ^{14}C MGK-264 After Topical Administration to Healthy Volunteers. Study No. P02058. S. Selim, Ph.D. Biological Test Center, Irvine, CA 92713., conducted for McLaughlin Gormley King Company, Martinez, CA 94553. Final Report Date: 6/18/92). Four healthy male volunteers were dermally administered 5.3 mg (~ 50 µCi) of ^{14}C labelled MGK-264 with 17.0 mg DEET and 1.0 mg MGK 326, to a 4 x 6 cm area on the volar aspect of the forearm. The area had a non-occlusive cover and 8 hours after application the dose was removed by wiping dosed area with isopropyl alcohol swabs. Blood samples were collected from both forearms (ipsilateral and contralateral) over 120 hours at regular intervals to determine levels of radioactivity in plasma. Urine and fecal samples were collected for 5 consecutive days and the skin was stripped (tape stripping) with 3M tape at 1, 23 and 45 hours after removal of the dosage. A mean of 0.39% of the administered radioactivity was excreted in the urine, most remained in the outer layer of the skin with no measurable amount in the feces. A total mean of 89.96 % was recovered. The tape stripping revealed that radioactivity did not accumulate in the skin. HPLC analysis of the urine demonstrated that the MGK 264 was extensively metabolized, however evaluation of the metabolism does not match the previous reports. No worksheet. Supplemental (P. Iyer, 7/14/97).

043 145097 “A Subchronic (3 - month) Inhalation Toxicity Study of MGK®-264 Insecticide Synergist in the Rat Via Whole-body Exposures,” P. Newton, Pharmaco::LSR Inc., NJ 08875 for McLaughlin Gormley King Company, MN. Study No 91-8364, 6/14/94. MGK®-264 Insecticide Synergist was administered by whole-body inhalation as a liquid aerosol to Sprague Dawley CD® rats (15/sex/group) for 6 hours/day, 5 days/week for 13 week at concentrations of 0, 0, 10, 40, 135 and 400 mg/m^3 in 1000 liter chambers. 7/sex/group of Groups 1 and 4 and 8/sex/group of groups 2 and 7 were allowed a 13 week recovery period. Daily examination revealed decreased activity during the exposures in the high dose group. Red facial stains, nasal discharge and excessive salivation was also noted in both sexes. The red facial stains were found during the entire exposure period while excessive nasal discharge occurred mainly at the high dose group and during the first two weeks. Reversible microscopic changes related to MGK® 264 exposure were noted as intracytoplasmic eosinophilic material in the epithelium covering the respiratory and /or olfactory mucosa of the nasoturbinates. An increased severity of hypertrophy/hyperplasia of the goblet cells in the nasopharynx of the high dose group was documented. Also observed was hyperplasia and hyperkeratosis of the stratified squamous epithelium of the larynx in the 135 mg/m^3 or 400 mg/m^3 groups. NOAEL = 135 mg/m^3 Acceptable (P. Iyer, 7/17/97).

028 131425 - Duplicate of 043 145097 “A Subchronic (3 - month) Inhalation Toxicity Study of MGK®-264 Insecticide Synergist in the Rat Via Whole-body Exposures,” P. Newton, Pharmaco::LSR Inc., NJ 08875 for McLaughlin Gormley King Company, MN. Study No 91-8364, 6/14/94.